EXHIBIT 1

Expert Report of John Flack, M.D., M.P.H.

I. Nature and Purpose of Report and Disclosures

This report is being offered pursuant to Federal Rule of Civil Procedure 26. Each of the opinions I have offered in this report is given to a reasonable degree of medical and scientific certainty. Additionally, each of my opinions is based on the materials I have reviewed in connection with this litigation, the methods and procedures of science, my knowledge of recognized medical and scientific principles and methodology reasonably relied upon by members of my profession, as well as my education, training, knowledge, and experience. Each opinion is offered to articulate a sufficiently reliable basis for my opinions concerning this case.

My curriculum vitae is attached as Exhibit A to this report. During the previous 4 years, I did not testify as an expert at trial or in a deposition outside of this litigation. My fees charged in connection with this engagement are consistent with my normal practice for such work. My work reviewing materials and preparing this report has been billed at $600 per hour. My hourly rate for deposition and trial testimony is $850.

A list of materials that I considered in rendering the opinions offered in this report is attached as Exhibit B. I reserve the right to supplement this list, as well as to amend and supplement the opinions expressed in this report. I also reserve the right to respond to and rebut all information provided in discovery, which I understand is ongoing, and any opinions offered by Plaintiffs' experts at their depositions or at trial.

Citations to specific reference material also are offered in this report, where I believe it necessary to cite a specific source; otherwise, my opinions are derived from a combination of reference sources, my experience, training, education and knowledge in the field. The facts and data set forth herein are the types of facts and data that I and other experts in my field reasonably rely upon. This report is not meant to be an exhaustive recitation of all my opinions as I understand they will be more fully explored in my deposition.[1]

I have been asked on behalf of Defendants to provide an independent analysis of whether trace amounts of N-nitrosodimethylamine ("NDMA") and N-nitrosodiethylamine ("NDEA") found in valsartan products could increase the risk of cancer in hypertension patients, such as Plaintiffs. I will offer opinions on hypertension generally, including its diagnosis and treatment, risk factors, epidemiology, secondary causes, and comorbidities, all of which relate to the underlying questions of causation. These opinions will include opinions on hypertension drug therapy, including use of valsartan, and the background of the valsartan recall. Additionally, I will opine on the epidemiology of hypertension and cancer, including the increased incidence of cancer in hypertension patients. I will also offer opinions on the medical and scientific literature on NDMA/NDEA and cancer, as well as valsartan and cancer, and Plaintiffs' claims of developing cancer allegedly as a result of using valsartan.

[1] This report is intended to offer opinions regarding general causation only, as requested by counsel. This report is not intended to be an exhaustive recitation of all of my opinions in this litigation, and I expressly reserve the right to amend or supplement this report to offer additional opinions, including opinions on liability, specific causation, damages, or other defenses, at the appropriate stage of litigation.

I have independently conducted a review and analysis of the literature on the above-listed topics, including in particular, but not limited to, the background risk factors for cancer in hypertension patients, the association between NDMA/NDEA and cancer, and the alleged relationship between valsartan use and cancer. In my regular practice and for purposes of my publications, I regularly research and analyze medical and scientific literature and rely on my education, training, and experience in the fields of internal medicine as well as epidemiology to form well-reasoned conclusions based on the available literature. I applied that same process to review and analyze the medical and scientific literature in this case.

I reserve the right to modify this report and my opinions as additional information is provided, including but not limited to additional discovery, medical records, expert reports, and the depositions of fact and expert witnesses.

II. Professional Education, Background and Accomplishments

I have served as the Professor and Chair of the Department of Internal Medicine at Southern Illinois University (SIU) for the past 6 years. I am also the Sergio Rabinovich Endowed Chair of Internal Medicine and Chief of the Hypertension Section in the Division of General Internal Medicine at SIU where I teach, conduct hypertension research, have an active hypertension clinical practice and lead the Department of Medicine (~50 million dollar annual budget). I am President of the American Hypertension Specialist Certification Program, serve as one of four Associate Editors at the American Journal of Hypertension, and chair the American Heart Association (AHA) Hypertension Professional Education and Publications Committee. I have published ~210 peer-reviewed manuscripts/book chapters and

my work has been cited over 14,000 times (Mendley Statistics). I have lifetime certification in Internal Medicine from the American Board of Internal Medicine (ABIM) as well as lifetime certification as a Specialist in Clinical Hypertension from the American Society of Hypertension.

In 1978, I earned a BS degree in Chemistry (Math minor) with distinction from Langston University. I subsequently entered the University of Oklahoma School of Medicine, graduating in 1982 with an MD degree; during medical school, I was elected to the Alpha Omega Alpha (AOA) Medical Honor Society. After graduation from medical school, I immediately entered the University of Oklahoma Internal Medicine residency training program that I completed in 1985; in 1985-86, I served as Chief Medical Resident for this training program. After two years as an Instructor on the University of Oklahoma Department of Medicine faculty, I left for the University of Minnesota School of Public Health, Division of Epidemiology where I completed a two-year National Institutes of Health post-doctoral fellowship in Cardiovascular Epidemiology. In 1990, I also earned a Master of Public Health (MPH) degree in Epidemiology from the University of Minnesota.

Throughout my career I have received numerous honors, served on various committees, and have provided professional service relevant to my expertise in hypertension and clinical trials. I served a multi-year term as a standing member of the U.S. Food and Drug Administration ("FDA") Cardio-Renal Advisory Panel and serve as an ad hoc reviewer for over 50 peer-reviewed medical journals (e.g., Hypertension [premier hypertension journal in the world], Journal of American Medical Association [JAMA], Journal of the American Society of Hypertension [JASH], Mayo Clinic Proceedings). I have also received numerous awards in my career, such

as being selected as one of the Detroit Super Doctors (2014), and repeatedly selected as one of the "Best Doctors in America", Michiganian of the Year (Detroit News, 2009), Academic Physician of the Year from the University of Oklahoma School of Medicine (2012), the American Heart Association F. Dewey Dodrill Award for Excellence (2007), and Crain's Detroit Business Health Care Hero Award for Outstanding Physician Achievement (2005).

Finally, I was asked and accepted an invitation to author the next *Hypertension* book chapter for the renowned Cecil's Textbook of Medicine. I am also currently authoring the chapter on *Initial Selection of Antihypertensive Drugs* for Up-to-Date (a recognized medical reference source used around the world). I have been recognized as an international expert and leading authority in hypertension.

A more detailed description of my academic and professional background and qualifications may be found in my curriculum vitae attached as Exhibit A.

III. Materials Reviewed

In my practice, I continuously review relevant medical literature as it is published, and as clinical issues come up that require re-review. The facts and data set forth below are of the type that I and other experts in my field reasonably rely upon. Many of my opinions expressed in this report are based on my cumulative knowledge from many years of hypertension practice and the literature I have reviewed over that time and on information I believe is generally known and accepted as true by those practicing in the hypertension community. During this engagement, I have reviewed the materials identified in Exhibit B.

IV. Definitions

ACE Inhibitor Angiotensin Converting Enzyme Inhibitor

ARB Angiotensin Receptor Blocker

ARNI Angiotensin Receptor Neprilysin Inhibitor

AHA American Heart Association

AMA American Medical Association

AOA Alpha Omega Alpha Medical Honor Society

ARNI Angiotensin Receptor Neprilysin Inhibitor (valsartan/saccabutril)

BS Bachelor of Science

BP blood pressure

DBP diastolic blood pressure

dl deciliter

eGFR estimated glomerular filtration rate

FMD fibromuscular dysplasia

mg milligrams

mm Hg millimeters of mercury

MD Medical Doctor

Meta-analysis a group of clinical trials that have been combined together and analyzed as a single study

PP pulse pressure (SBP – DBP)

SBP systolic blood pressure

SIU Southern Illinois University School of Medicine

SMR Standardized Mortality Ratio

≥ Equal to or greater than

≤ Equal to or less than

V. Hypertension Generally

A. What Is Hypertension?

Hypertension, or elevated blood pressure, occurs when the pressure inside the arterial blood vessels consistently exceeds 130/80 mmm Hg. Indirect estimation of the blood pressure level is most commonly done by applying an appropriate size blood pressure cuff over a bare arm (just above the elbow) to compress the brachial artery which stops the normal continuous flow of blood. The cuff is deflated slowly and when the external pressure falls below the blood pressure in the brachial artery, the return of pulsating sound (Korotkoff sounds) marks the level of systolic BP. At this point, the flow of blood in the brachial artery is episodic, not continuous. As the BP cuff further deflates, the flow of blood in the brachial artery ultimately becomes continuous at which point the Korotkoff sounds disappear – this marks the level of diastolic blood pressure. Thus, every individual has a systolic (top number) and diastolic blood pressure (bottom number) – for example, 120/80 mm Hg.

B. Blood Pressure Classifications/Stages of Hypertension

The 2017 American College of Cardiology (ACC)/American Hypertension Association (AHA) hypertension guideline[2] revised how we classify blood pressure levels. *Normal* is considered to be less than 120 systolic and less than 80 mm Hg diastolic; *Elevated* is when systolic blood pressure is between 120 – 129 and diastolic blood pressure is less than 80 mm Hg; *Stage 1 hypertension* is when systolic blood

[2] Whelton PK et al., 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, Hypertension 2018;71:e13-e115.

pressure is 130 – 139 and diastolic blood pressure is 80 – 89 mm Hg; and *Stage 2 hypertension* is when systolic blood pressure is 140 or higher and diastolic blood pressure is 90 mm hg or higher. When the systolic and diastolic blood pressures fall into different categories, the highest category determines the blood pressure classification or stage of hypertension. BP 138/110 mmm Hg, for example, would be stage 2 hypertension.

Blood pressure categories and stages of hypertension have therapeutic significance. In adults with elevated, stage 1, or stage 2 hypertension, lifestyle modifications (weight loss, sodium and alcohol restriction, and physical activity increase) should be provided. And though hypertension is diagnosed when blood pressure exceeds the 130/80 mm Hg threshold, only high-risk hypertensives actually qualify for drug therapy in stage 1 hypertension; the majority (~70%) of all hypertensives do not qualify for drug therapy until they reach stage 2 hypertension.[3]

C. Hypertension Risk Factors

Hypertension risk factors include obesity/rapid weight gain, physical inactivity, excessive alcohol intake (> 2 drinks/d in men, > 1 drink/d in women), and high dietary sodium intake. Accordingly, weight loss, increased physical activity, reductions in alcohol intake, and decreased intake of dietary sodium have been shown to lower blood pressure. The ACC/AHA hypertension guideline recommends

[3] Muntner P et al., Potential US population impact of the 2017 ACC/AHA high blood pressure guideline, Circulation 2018;137(2):109-118.

counseling on diet and lifestyle modifications for all adults with elevated blood pressure (SBP 120 – 129 and DBP less than 80 mm Hg) and hypertension.[4]

D. Epidemiology of Hypertension

According to the AHA/ACC 2017 hypertension guideline ~116 million US adults or 45.6% of the adult population age 20 years and older have hypertension.[5] Importantly, this guideline—for the first time—used the BP threshold of 130 (systolic) and/or 80 mm Hg (diastolic) as the level above which drug naïve individuals would be diagnosed as having hypertension; up until late 2017, the diagnostic BP threshold for hypertension had been 140/90 mm Hg. SBP rises with advancing age while DBP plateaus in the 6th decade of life and, on average, declines thereafter; this leads to wide pulse pressure hypertension that most commonly occurs amongst older hypertensives. Women are more frequently affected by hypertension than men. The highest geographic prevalence of hypertension in the US is in the southeastern geographical area, also known as the stroke belt. 54.9%, 47.3%, 34.4%, and 36.5%, respectively, of Non-Hispanic blacks, Non-Hispanic whites, Hispanics, and Non-Hispanic Asians have hypertension.[6]

[4] Whelton PK et al., 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, Hypertension 2018;71:e13-e115.
[5] *Id.*; Muntner P et al., Potential US population impact of the 2017 ACC/aHA high blood pressure guideline, Circulation 2018;137(2):109-118.
[6] Whelton PK et al., 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, Hypertension 2018;71:e13-e115.

E. Secondary Causes of Hypertension

The vast majority of adults with hypertension have essential hypertension. Essential hypertension refers to elevated blood pressure readings that are not directly linked to a specific known secondary cause. Major secondary causes of hypertension can manifest in persons who have previously had normal blood pressure, though when secondary causes occur in adults, especially beyond the mid 40's, they often occur super-imposed on essential hypertension.

Major causes of secondary hypertension include:

1) *Obstructive Sleep Apnea*: this condition is seen much more commonly in men than women and is the most common type of secondary hypertension. And though obesity is an important risk factor for this condition, sleep apnea can occur in lean individuals as well. Sleep apnea is characterized by intermittent upper airway obstruction that leads to sympathetic nervous system activation, fragmented sleep patterns, elevated blood pressure, and increased risk for cardiovascular disease. The gold standard treatment for sleep apnea is continuous positive airway pressure (CPAP), a device worn during sleep that helps prevent upper airway collapse and therefore the obstructions that characterize sleep apnea. Some patients with sleep apnea do not tolerate CPAP therapy so we recommend that they get fit for an oral appliance that pulls forward the lower jaw thus decreasing the likelihood of intermittent upper airway collapse during sleep.

2) *Primary Aldosteronism*: primary aldosteronism is the second most common cause of secondary hypertension. This condition is characterized by autonomous secretion of aldosterone from one or both adrenal glands that leads to salt and water

retention, constriction of blood vessels, elevated blood pressure and severe target-organ injury – left ventricular hypertrophy/heart failure, kidney dysfunction, stroke, and myocardial infarction (heart attack). The excessive, autonomous hyper-secretion of aldosterone occurs bilaterally in ~two-thirds of cases and unilaterally in the other one-third. Those with unilateral hypersecretion are typically candidates for laparoscopic adrenalectomy, a procedure that cures the hypertension in ~50% of patients. In those who are not cured after adrenalectomy, BP is typically lower and can be more easily controlled with fewer medications. Primary aldosteronism patients with bilateral hypersecretion of aldosterone are not surgical candidates and are therefore managed medically with stringent dietary sodium restriction, and antihypertensive drug therapy (thiazide diuretics, aldosterone antagonists, calcium antagonists, ACE inhibitors, ARBs).

3) Renal Artery Stenosis (Renovascular Hypertension): obstruction of one or both arteries leading to the kidneys, which if significant enough (termed critical renal artery stenosis) can cause elevated blood pressure and, if affecting both kidneys, can also cause kidney dysfunction. The most common cause of renal artery obstruction is the build-up of atherosclerotic plaque, although there are other uncommon causes of obstruction (e.g., renal artery dissection). Most patients with critical renal artery stenosis do not respond to renal revascularization (angioplasty + stenting) with any discernable improvement in blood pressure. Accordingly, based on the best available clinical trial evidence, the most recent ACC/AHA hypertension guideline does not recommend screening for critical renal artery stenosis except in patients with heart failure/recurrent flash pulmonary edema, refractory hypertension, and/or reduced/worsening kidney function (ischemic nephropathy). Another form of critical

renal artery stenosis is called fibromuscular dysplasia (FMD). FMD is, though, much less common than atherosclerotic renal artery stenosis. FMD preferentially affects women and does respond to angioplasty of the affected renal artery (without stenting) with prompt reductions in blood pressure. FMD is caused by an intrinsic renal artery abnormality that causes the vessel to intermittently narrow resulting in the classic "string of pearls" appearance of renal arterial angiograms. We infrequently pursue the diagnosis of critical renal artery stenosis except in the patient types as described in the ACC/AHA hypertension guideline.

4) Pheochromocytoma: this is a very rare but devastating form of secondary hypertension. The primary abnormality in pheochromocytoma is hypersecretion of catecholamines (norepinephrine, epinephrine, dopamine), typically from the adrenal gland(s) although occasionally the anatomic source of the hyper-secretion can be extra-adrenal in origin. Clinically patients have signs, at least intermittently, of sympathetic nervous system activation including spikes in blood pressure, very rapid heartbeat, sweating, and anxiety. Pheochromocytoma is rare. Untreated or inadequately treated obstructive sleep apnea can mimic pheochromocytoma as both conditions augment sympathetic nervous system activity and can cause similar clinical symptoms.

F. Hypertension Risk Stratification

The 2017 ACC/AHA hypertension guideline outlined a somewhat different approach to risk-stratifying hypertensive patients than was previously

recommended.[7] The basic premise of the new recommendation was that *high-risk* hypertensives would be treated sooner (at a lower blood pressure level) than lower risk hypertensives. The rationale for this recommendation was that meta-analyses of hypertension studies have shown that the absolute cardiovascular risk reduction was directly related to the magnitude of pre-treatment cardiovascular risk.[8] Pre-treatment cardiovascular risk is not solely a consequence of hypertension severity but is also related to the presence of certain co-morbidities as well as the presence of known cardiovascular disease. Thus, the greater cardiovascular risk reduction with drug therapy in *high-risk* hypertensives is the compelling reason for treating them sooner.

High-risk in individuals with hypertension is defined by the presence of at least of the following: 1) age 65 years or older; 2) known cardiovascular disease (e.g., heart failure, prior myocardial infarction or stroke); 3) diabetes mellitus; 4) chronic kidney disease (estimated glomerular filtration rate less than 60 ml/min/1.73 m^2 and/or urine albumin/creatinine ratio of 300 mg/g or greater or prior kidney transplant); or 5) 10-year atherosclerotic cardiovascular disease risk of 10% or higher.

Thus, high-risk hypertensives qualify for drug therapy when their blood pressure is 130/80 mmm Hg or higher; lower risk hypertensives qualify for drug

[7] Whelton PK et al., 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, Hypertension 2018;71:e13-e115.

[8] van der Leeuw J et al., Personalized cardiovascular disease prevention by applying individualized prediction of treatment effects, Eur Heart J. 2014;35(13):837-843; Baker S et al., Using thresholds based on risk of cardiovascular disease to target treatment for hypertension: modelling events averted and number treated, BMJ, 2000;320(7236):680-685 [published correction appears in BMJ 2000 May 27;320(7247):1436].

therapy when their blood pressure is 140/90 mm Hg or higher. Most hypertensives, including both high- and low-risk individuals, are treated to a target of less than 130/80 mm Hg, although for individuals 65 years of age and older, only a systolic blood pressure target was given (less than 130 mm Hg).

G. Hypertension Control Rates

Nearly 82 million or 36.2% of US adults qualify for immediate antihypertensive drug therapy.[9] 53.4% of drug-treated hypertensive adults have BP $\geq$ 130/80 mm Hg.[10] Using the 140/90 mm Hg threshold, the hypertension control rate declined to 43.7% (2017 – 2018) from 53.8% (2013 – 2014).[11] BP control was highest in adults aged 45 – 64 years of age but was lower at both extremes of age. Controlled BP was documented in 48.2% of non-Hispanic Whites, versus 41.5% of non-Hispanic Blacks; control rates were also higher in those with private insurance (48.2%) and Medicare (53.4%) versus those with government insurance other than Medicare or Medicaid (43.2%).[12] Thus, hypertension control in the US population is sub-optimal and manifests significant disparities by race/ethnicity and insurance status.

H. Major Hypertension Outcomes

Hypertension is a major, treatable risk factor for premature death, stroke, heart failure, chronic kidney disease [CKD]/end-stage renal disease [ESRD], myocardial infarction, peripheral vascular disease, and dementia. These risks

[9] Muntner P et al., Potential US population impact of the 2017 ACC/AHA high blood pressure guideline, Circulation 2018;137(2):109-118.
[10] *Id.*
[11] Muntner P et al., Trends in Blood Pressure Control Among US Adults with Hypertension, 1999-2000 to 2017-2018, JAMA 2020;324(12):1190-1200.
[12] *Id.*

attributable to blood pressure elevations do not magically appear when the BP is high enough to be considered hypertension. Rather, there is a graded, continuously escalating risk of these outcomes that begins well within the normal range as BP increases above 115/75 mm Hg. This risk for adverse cardiovascular outcomes doubles for every 20/10 mm Hg higher BP above 115/75 mm Hg. Accordingly, not all adults at increased risk for the adverse health effects of hypertension are recommended for or undergoing antihypertensive drug therapy.

I. Hypertension Co-morbidities

In general, patients with hypertension are not as healthy as other people and often have comorbidities. Hypertension occurs commonly in persons with diabetes and chronic kidney disease. In fact, approximately 80% of adults with these two co-morbid conditions have hypertension. The coexistence of hypertension and diabetes occurs, in no small part, because of common risk factors such as obesity, physical inactivity, and a calorie-replete diet. Hypertension and chronic kidney disease occur together because not only is hypertension a risk factor for CKD but also, the more kidney function deteriorates, the greater likelihood of hypertension; this is likely due to the inability to maintain normal salt and water homeostasis as kidney function worsens in persons with sodium-replete diets. Persons with known cardiovascular disease (e.g., heart failure, stroke) often have hypertension because elevated BP is a known risk factor for most cardiovascular diseases.

Importantly, the presence of the above hypertension co-morbidities substantively impacts the recommended approach to antihypertensive treatment. First, diabetes, chronic kidney disease, and cardiovascular disease, when present in

hypertensives, place them in the high-risk category, meaning that they qualify for antihypertensive drug therapy when their BP is consistently at or above 130 systolic and/or 80 mm Hg diastolic. Second, these conditions have all been linked to pharmacological resistance to antihypertensive drug therapy, meaning that a greater intensity of drug therapy will be needed to achieve BP control. Third, the presence of selected co-morbidities in persons with hypertension impacts antihypertensive drug selection. For example, in those with CKD, ACE inhibitors or ARBs should be included in the antihypertensive drug treatment regimen because they have been proven to slow the progressive decline over time in kidney function. Amongst patients with heart failure, both those with reduced as well as preserved ejection fraction, ACE inhibitors or ARBs, along with beta blockers and aldosterone antagonists, reduce morbid and fatal events and are thus preferred therapies. New data with angiotensin receptor neprilysin inhibitors (ARNIs) have shown the superiority of this drug class relative to ACEs and ARBs in heart failure patients, both with reduced and preserved ejection fraction.

J. Diagnosing Hypertension

The diagnosis of hypertension is most commonly made when there are sustained blood pressure elevations that are documented over temporally spaced time points of measurement. Often, though not always, this occurs in a physician's office. The optimal approach is to use a standard measurement protocol, obtain multiple blood pressure readings to be averaged, and repeat this over time. The diagnosis of hypertension is made when blood pressure consistently is 130 and/or 80 mmm Hg or higher. Ideally, this should be the average of multiple blood pressure readings at each visit across multiple (at least 2) visits. The exception to this is when

blood pressure is 180 systolic and/or 110 mm Hg diastolic or higher, in which case the diagnosis of hypertension is confirmed and drug therapy should be started immediately.

K. Accurate BP Measurement

Accurate measurement of BP is imperative for making sound therapeutic decisions regarding antihypertensive drug therapy. However, accurate BP measurement in any setting does not occur without purposeful intent. First, validated BP devices should be used when taking BP. Second, a standard measurement protocol should be followed as summarized in the Target-BP program [quiet room/no conversation, empty bladder, use correct cuff size, place BP cuff on bare arm, support arm at heart level, keep legs uncrossed, and support back and feet.][13] Finally, multiple BP measurements should be obtained, spaced ~1 minute apart and averaged. Adherence to the aforementioned approach results in BP readings that are systematically lower than usual office BP readings. One study by Egan and colleagues reported an 11/5 mm Hg lower BP in uncontrolled hypertensives after implementing a rigorous BP measurement protocol in the absence of any changes to medications.[14]

Despite accurate measurement of BP being required for making sound diagnostic decisions, very few clinics utilize rigorous BP measurement protocols. The most likely explanation is that rigorous BP measurement protocols change workflow, as you cannot measure an accurate BP as quickly as you can a spuriously high one

[13] How to accurately measure blood pressure at home, www.heart.org, *available at* https://www.heart.org/en/news/2018/05/01/aha-ama-launch-high-blood-pressure-initiative (last accessed July 29, 2021).
[14] Egan BM et al., Improving Hypertension Control in Primary Care with the Measure Accurately, Act Rapidly, and Partner with Patients Protocol, Hypertension 2018;72(6):1320-1327.

obtained by usual means. However, there are multiple benefits when BP is measured accurately: 1) hypertension is not spuriously diagnosed; 2) hypertension severity is not overestimated; 3) white coat hypertension/effect is minimized; 4) over-medication of patients is avoided; and 5) in-office BP control rates are substantively higher.

L. Initial Patient Evaluation

The ACC/AHA hypertension guideline provides excellent guidance regarding the initial patient evaluation for patients with hypertension.[15] First and foremost, every patient should have a comprehensive history and physical examination performed. Examples of important history to obtain include the duration of hypertension, medication history, the range of blood pressure levels since diagnosis, dietary patterns, physical activity, alcohol intake, snoring/the presence of daytime sleepiness, history of low potassium level, all medications (prescribed as well as those drugs obtained over the counter), family history of early onset hypertension in first degree relatives (before 25 years of age) and/or stroke (before 40 years of age). Available medical records, including clinic notes, laboratory and diagnostic tests should be reviewed. At the initial visit, multiple blood pressure readings should be obtained (1 minute apart) and averaged in both arms as well as in both the seated and standing positions (checking for orthostatic hypotension). The arm with the

[15] Whelton PK et al., 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, Hypertension 2018;71:e13-e115.

highest averaged BP reading should be used for BP measurements at subsequent clinic visits.

Recommended basic testing includes: 1) fasting blood glucose, 2) complete blood count, 3) lipid profile, 4) serum creatinine with eGFR, 5) serum sodium, potassium and calcium, 6) thyroid stimulating hormone, 7) urinalysis, and 8) electrocardiogram. Optional testing includes: 1) echocardiogram, 2) uric acid, and 3) urinary albumin:creatinine ratio. In my clinical practice, I typically obtain a hemoglobin A1C in every patient as this allows the diagnosis of pre-diabetes and diabetes without the need for fasting – this is a better test than fasting glucose for making these diagnoses. Also, I measure uric acid and urine albumin:creatinine ratio in all patients with hypertension at their initial evaluation. The rationale is that there is considerable evidence of a BP lowering effect of allopurinol, a xanthine oxidase inhibitor that lowers serum uric acid, when given to individuals with serum uric acid > 5.5 mg/dl. And, there is good evidence that allopurinol reduces risk for stroke and myocardial infarction and also slows/prevents the decline in kidney function in patients with depressed kidney function. Thus, I frequently prescribe allopurinol to my patients with hypertension when their serum uric acid is 5.5 mg/dl or higher. Finally, the urine albumin:crea ratio (measured in a spot urine) is needed to determine if chronic kidney disease is present in patients with eGFR $\geq$ 60 ml/min/1.73 m^2, and, in patients with known CKD, when this ratio is $\geq$ 300 mg/d, an ACE inhibitor or ARB should be included preferentially in the antihypertensive drug regimen.

M. Patient Counseling

In diagnosing and treating hypertensive patients, I regularly counsel patients on the following topics:

Hypertension Disease Conditions/Symptoms: I always counsel patients regarding why their hypertension is being treated. That is, to prevent premature mortality as well as to reduce the risk for heart failure, stroke, myocardial infarction, peripheral arterial disease, kidney dysfunction/failure, and cognitive decline/dementia. And though hypertension has been labeled the "silent killer", it does cause side effects in some patients. For example, it is well known and accepted that headache can occur as a consequence of elevated BP. However, hypertension has also been linked to sleep disturbance and shortness of breath.[16] The BP number is important: the higher the BP, the higher the risk for these complications and also the greater the absolute risk benefit from successful drug therapy.

Diet and Lifestyle Changes: I also discuss what the patient can do with their diet and lifestyle, along with taking their prescribed medications, to lower their BP. The greater adoption of effective and lifestyle interventions, the more effective antihypertensive drug therapy will be or the less intensive drug treatment will need to be to achieve target BP levels. Although dieticians are available in ambulatory and hospital settings, in ambulatory clinic settings patients may never be referred to a

[16] Flack JM et al., The rapidity of drug dose escalation influences blood pressure response and adverse effects burden in patients with hypertension: the Quinapril Titration Interval Management Evaluation (ATIME) Study, ATIME Research Group, Arch Intern Med. 2000;160(12):1842-1847.

dietician by the provider or, if referred, may not attend scheduled sessions if their insurance plan does not cover it.

Dietary Sodium Restriction: sodium is widely present in a typical western society diet in amounts far above what is needed to meet physiological needs. The average American adult consumes ~3400 mg (3.4 grams or 148 mmols of sodium per day). High dietary sodium intake antagonizes the pharmacologic BP reductions attainable with most antihypertensive drug classes. There is no credible evidence that lowering dietary sodium intake, even drastically, harms patients. Current recommendations for daily dietary sodium intake range from 1500 mg (65.2 mmol) to 2500 mg (109 mmol) per day. Approximately 70 – 75% of dietary sodium is processed into the foods we eat prior to consumption. The following are common examples of high sodium foods: breads, soups, processed meats (e.g., bacon, salami, ham, sausage), fast foods, pickles, pizza, and frozen dinners.

Other Lifestyle Modifications: Certain lifestyle modifications proven to lower BP include the following: 1) limiting alcohol intake to no more than 2 drinks per day in men and no more than 1 drink per day in women, 2) weight loss, 3) increased physical activity (especially aerobic activity), 4) increased dietary consumption of potassium, and 5) increased consumption of vegetable protein.

Medication Adherence and Risks/Benefits: Another important conversation I have with patients is regarding adherence to the medications they have been prescribed. Studies have shown that at least 20% of patients never start taking

newly initiated hypertensive medications,[17] and of those who do start taking their medication, approximately 50% have stopped taking them within a year[18]. Antihypertensive medications have to be taken continuously to effectively lower BP. I also warn patients when taking certain drugs (e.g., beta blockers, central adrenergic inhibitors) that if they abruptly stop them, that they might conceivably experience a dangerous, dramatic rise in BP (rebound hypertension). Further, we counsel patients to avoid conflating hypertension condition/treatment symptoms with true adverse drug effects.

We also discuss with patients the risks and benefits of the prescribed antihypertensive medication. The primary benefits of an antihypertensive drug regimen include lowering BP and thus lowering the risk of suffering the major hypertension outcomes identified above (i.e., premature death, stroke, heart failure, chronic kidney disease [CKD]/end-stage renal disease [ESRD], myocardial infarction, peripheral vascular disease, and dementia). The risks, or potential side effects, associated with antihypertensive drugs are dependent on the particular drug prescribed but often include minor side effects, such as skin photosensitization and muscle cramps (thiazide diuretics); fatigue (beta blockers); dry non-productive cough (ACE inhibitors); lower extremity edema (dihydropyridine calcium antagonists) and even potentially severe side effects such as angioedema (ACE inhibitors) and skin cancer (thiazide diuretics).

[17] Fischer MA et al., Trouble getting started: predictors of primary medication nonadherence, Am J Med. 2011;124(11):1081.e9-1081.e1.081E22.
[18] Vrijens B et al., Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories, BMJ 2008;336(7653):1114-1117.

N. Hypertension Drug Therapy

Antihypertensive Drugs Generally: When patients qualify for antihypertensive drug therapy for the first time, there are several decisions that must be made. First, how many antihypertensive drugs will be prescribed? According the ACC/AHA hypertension guideline, the choice is either one or two drugs – prescribed as two separate pills or as a single pill combination.[19] It is recommended that two drug therapy be initiated in those with BP > 20/10 mm Hg above their target (typically <130/80 mm Hg), in most black patients, and should also be considered in patients with stage 2 hypertension (SBP $\geq$ 140 and/or DBP $\geq$ 90 mmm Hg). Fewer than 25% of drug-treated adult hypertensives within the USA are treated with more than 2 antihypertensive drugs.[20] Second, from which drug classes should initial drug therapy be selected? The ACC/AHA guideline recommends four initial drug classes as appropriate for initial therapy: 1) thiazide diuretics, 2) ACE inhibitors, 3) ARBs, and 4) calcium antagonists. The most effective two-drug combinations are either an ACE inhibitor or ARB + thiazide diuretic, or an ACE inhibitor or ARB + calcium antagonist. Once drug therapy has been initiated, patients should be evaluated approximately monthly for up-titration of their drugs if their BP remains above goal. Patients started on a thiazide diuretic and/or either an ACE inhibitor or ARB are often seen within a couple of weeks of starting treatment to check their serum electrolytes (e.g., serum sodium, potassium) and kidney function (creatinine, eGFR), both of

[19] Whelton PK et al., 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, Hypertension 2018;71:e13-e115.
[20] Derington CG et al., Trends in Antihypertensive Medication Monotherapy and Combination Use Among US Adults, National Health and Nutrition Examination Survey 2005-2016, Hypertension 2020;75(4):973-981.

which can be adversely impacted by these two drug classes. However, long-acting antihypertensive drugs with long therapeutic half-lives take many weeks to manifest their full BP lowering effect, thus the recommendation is to intensify antihypertensive drug therapy, in most patients, no more frequently than approximately monthly. Once hypertension is controlled patients should be seen again every 3 – 6 months.

Role of Angiotensin Receptor Blockers in Contemporary Antihypertensive Drug Therapy: As of the publication of the ACC/AHA hypertension guideline in early 2018, there were 8 different ARBs and 10 ACE inhibitors approved by the FDA for the treatment of hypertension in the USA. ARBs and ACE inhibitors are considered mostly interchangeable as it relates to their benefits in heart failure (reduced ejection fraction) and chronic kidney disease (CKD), two conditions for which both drug classes have proven clinical benefit that is not solely explained by their ability to lower BP. Nevertheless, there are differences between these two drug classes that mostly relate to drug-related side effects. Angiotensin receptor antagonists (ARBs) have a tolerability profile comparable to placebo. Notably, ARBs do not have dose-related side effects (more side effects at higher doses).[21] Valsartan, losartan, and irbesartan are ARBs. ACE inhibitors, on the other hand, can cause angioedema and cough, while ARBs do not. ARBs and ACE inhibitors lower BP to a similar degree. ARBs as a drug class have previously been linked to an increase in risk for cancer;

[21] Pool JL et al., Dose-response efficacy of valsartan, a new angiotensin II receptor blocker, J. Hum. Hypertens. 1999;13(4):275-281; Brunner HR, Clinical efficacy and tolerability of Olmesartan. Clin. Ther. 2004;26 Suppl A:A28-A32.

however, this link was ultimately rejected by the FDA based on an extensive evaluation of clinical trial and observational data.[22]

O. Epidemiology of Hypertension and Cancer

Case-control and cohort studies[23] have reported higher incidence of cancer risk amongst hypertensives, both medicated[24] and un-medicated,[25] across varied cell-types (e.g., squamous cell carcinoma, adenoma carcinoma). BP level has been linked to increased risk of some cancers, including kidney cancer.[26] In addition, obese hypertensives have an augmented risk for kidney cancer compared to lean (BMI < 23) hypertensives.[27]

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[22] Sipahi I et al., Angiotensin-receptor blockade and risk of cancer: meta-analysis of randomised controlled trials, Lancet Oncol. 2010;11(7):627-636; Bangalore S et al., Antihypertensive drugs and risk of cancer: network meta-analyses and trial sequential analyses of 324,168 participants from randomised trials, Lancet Oncol. 2011;12(1):65-82; ARB Trialists Collaboration. Effects of telmisartan, irbesartan, valsartan, candesartan, and losartan on cancers in 15 trials enrolling 138,769 individuals, J Hypertens. 2011;29(4):623-635; Pasternak B et al., Use of angiotensin receptor blockers and the risk of cancer, Circulation 2011;123(16):1729-1736.

[23] Colt JS et al., Hypertension and risk of renal cell carcinoma among white and black Americans, Epidemiology 2011;22(6):797-804; Han H et al., Hypertension and breast cancer risk: a systematic review and meta-analysis, Sci Rep. 2017;7:44877; Hidayat K et al., Blood pressure and kidney cancer risk: meta-analysis of prospective studies, J Hypertens. 2017;35(7):1333-1344; Largent JA et al., Hypertension, diuretics and breast cancer risk. J Hum Hypertens. 2006;20(10):727-732; Seretis A et al., Association between blood pressure and risk of cancer development: a systematic review and meta-analysis of observational studies, Sci Rep. 2019;9(1):8565.

[24] Colt JS et al., Hypertension and risk of renal cell carcinoma among white and black Americans, Epidemiology 2011;22(6):797-804; Largent JA et al., Hypertension, diuretics and breast cancer risk, J. Hum. Hypertens. 2006;20(10):727-732; Seretis A et al., Association between blood pressure and risk of cancer development: a systematic review and meta-analysis of observational studies, Sci Rep. 2019;9(1):8565.

[25] Kim CS et al., Association of hypertension and blood pressure with kidney cancer risk: A nationwide population-based cohort study, Hypertension 2020;75:1439-1446; Chow WH et al., Obesity, hypertension, and the risk of kidney cancer in men, N. Engl. J. Med. 2000;343:1305-1311.

[26] Colt JS et al., Hypertension and risk of renal cell carcinoma among white and black Americans, Epidemiology 2011;22(6):797-804; Hidayat K et al., Blood pressure and kidney cancer risk: meta-analysis of prospective studies, J Hypertens. 2017;35(7):1333-1344.

[27] Kim CS et al., Association of hypertension and blood pressure with kidney cancer risk: A nationwide population-based cohort study, Hypertension 2020;75:1439-1446; Chow WH et

A recently published study by Christakoudi and co-workers from the European Prospective Investigation into Cancer and Nutrition (EPIC) involving over 300,000 men and women followed for an average of 13.7 years found positive associations between higher BP with renal cell carcinoma and esophageal squamous cell carcinoma as well as weaker associations with head and neck cancers, skin squamous cell carcinoma, colon cancer, post-menopausal breast cancer and uterine adenocarcinoma.[28] They also reported weak inverse associations of SBP with lymphomas and cervical squamous cell cancer.[29]

Additionally, some site-specific cancers may be increased such as kidney cancer along with, in women, pancreatic and endometrial cancers.[30] Lung cancer risk appears to be lower in hypertensives[31] while liver cancer risk is higher (22.9%)[31b,31c].

Thus, the heightened risk for cancer amongst adults with hypertension/higher BP occurs across different cancer cell types and anatomic locations; however, because some cancers are more and less common in hypertensives, their overall cancer risk may not always be elevated.

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al., Obesity, hypertension, and the risk of kidney cancer in men, N. Engl. J. Med. 2000;343:1305-1311.

[28] Christakoudi S et al., Blood pressure and risk of cancer in the European Prospective Investigation into Cancer and Nutrition, Int. J. Cancer 2020;146(10):2680-2693.

[29] *Id.*

[30] Lindgren AM et al., Cancer pattern among hypertensive patients in North Karelia, Finland J. Hum. Hypertens, 2005;19(5):373-379.

[31] *Id.*

[31b] Kasmari AJ, et al., Independent of Cirrhosis, Hepatocellular Carcinoma Risk Is Increased with Diabetes and Metabolic Syndrome. Am J Med. 2017;130(6):746.e1-746.e7.

[31c] Seretis A et al., Association between blood pressure and risk of cancer development: a systematic review and meta-analysis of observational studies. Sci Rep. 2019;9(1):8565. Published 2019 Jun 12.

The explanations of the hypertension and cancer epidemiological association have been multiple, though it is unclear which one is most explanatory. First, adult patients with hypertension also have co-morbidities, such as diabetes[32] and obesity, both of which are associated with heightened cancer risk. In 104,343 Taiwanese adults with diabetes followed between 1998 – 2009, diabetes mellitus was an independent risk factor, along with hypertension, for liver cancer.[33] Additionally, hepatitis C infection affects ~1% of the global population and is the major risk factor for hepatocellular carcinoma; the global incidence of new hepatitis C cases was 23.7 cases per 100,000 population in 2015 with approximately 10 – 20% developing cirrhosis or hepatocellular carcinoma.[34] Second, hypertension and cancer share common risk factors, such as alcohol intake, diet and physical inactivity; low physical activity, for example, is a risk factor for both kidney[35] and bladder cancer[36], while habitually high dietary salt intake has been linked to gastric cancer risk[37]. Third, certain antihypertensive drugs have been linked to augmented cancer risk—notably, calcium antagonists have been linked with prostate cancer,[38] and multiple antihypertensive drug classes including ACE inhibitors, ARBs, calcium antagonists,

[32] Giovannucci E et al., Diabetes and cancer: A consensus report, Diabetes Care 2010;33:1674-1685.
[33] Kasmari AJ et al., Independent of Cirrhosis, Hepatocellular Carcinoma Risk Is Increased with Diabetes and Metabolic Syndrome, Am J Med. 2017;130(6):746.e1-746.e7.
[34] Spearman CW et al., Hepatitis C, Lancet 2019; 394:1451 – 1466.
[35] Behrens G et al., The association between physical activity and renal cancer: systematic review and meta-analysis, Br. J. Cancer 2013;108(4):798-811.
[36] Keimling M et al., The association between physical activity and bladder cancer: systematic review and meta-analysis, Br. J. Cancer 2014;110(7):1862-1870.
[37] D'Elia L et al., Habitual salt intake and risk of gastric cancer: a meta-analysis of prospective studies, Clin. Nutr. 2012;31(4):489-498.
[38] Cao L et al., Antihypertensive drugs use and the risk of prostate cancer: a meta-analysis of 21 observational studies, BMC Urology 2018;18:17.

and diuretics have been linked to kidney cancer and/or bladder cancer[39]. However, the detection of elevated cancer risk amongst un-medicated hypertensives means that antihypertensive drugs, per se, do not explain entirely the linkage of certain cancers with hypertension. Fourth, drug exposures to agents used to treat hypertension co-morbidities have been linked to cancer—for example, the drug metformin (reduced risk), as well as insulin therapy (increased risk), used to treat diabetes have been linked to liver cancer, as have various cholesterol-lowering medications (reduced risk).[40] Fifth, it is possible, though not widely believed plausible, that hypertension might directly increase the risk of malignant cell transformation.[41] Thus, there are a multiplicity of factors that influence the risk of cancer in patients with hypertension.

VI. Valsartan for Effective Hypertension Treatment

As discussed above, valsartan is one of many ARBs that is commonly used for hypertension treatment. Valsartan is available in four different dosage strengths: 40 mg, 80 mg, 160 mg, and 320 mg. In my experience, valsartan is a safe medication that is effective in treating and controlling hypertension. I personally have prescribed valsartan to many patients, and those patients have had successful outcomes, including lower blood pressure and reduced hypertension symptoms, while taking valsartan.

[39] Xie Y et al., Antihypertensive medications are associated with the risk of kidney and bladder cancer: a systematic review and meta-analysis, Aging 2020;12(2):1545-1562.
[40] Kasmari AJ et al., Independent of Cirrhosis, Hepatocellular Carcinoma Risk Is Increased with Diabetes and Metabolic Syndrome, Am. J. Med. 2017;130(6):746.e1-746.e7.
[41] Giordano G et al., Postmenopausal status, hypertension and obesity as risk factors for malignant transformation in endometrial polyps. Maturitas. 2007;56(2):190-197.

VII. Valsartan Recall and Impact on Hypertension Patients

In July 2018, manufacturers of medications containing the active pharmaceutical ingredient valsartan began initiating voluntary recalls of their products after certain lots were found to contain trace amounts of the unexpected impurity NDMA.[42] In November 2018, another unexpected impurity, NDEA, was found in trace amounts of valsartan products, and as a result, additional voluntary recalls were initiated by the manufacturers of the valsartan products at issue. Nitrosamines, such as NDMA and NDEA, are commonly found in everyday products and sources; for example, as the FDA has recognized, nitrosamines are present "in water and foods, including cured and grilled meats, dairy products and vegetables."[43] The FDA has thus estimated that the additional risk posed by ingesting valsartan containing NDMA or NDEA is extremely low—specifically, according to FDA, "if 8,000 people took the highest valsartan dose (320 mg) containing N-Nitrosodimethylamine (NDMA) from the recalled batches daily for four years [amount of time the FDA believed NDMA-containing valsartan was on the US market before recall], there may be one additional case of cancer over the lifetimes of those 8,000 people."[44] And, as the FDA has recognized, that estimate likely overstates the actual risk, as the majority of patients taking valsartan are not prescribed the maximum dose of 320 mg. Moreover,

[42] Center for Drug Evaluation and Research, ARB Recalls: Valsartan, Losartan and Irbesartan. U.S. Food and Drug Administration, *available at* https://www.fda.gov/drugs/drug-safety-and-availability/recalls-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and-irbesartan (last visited July 6, 2021).

[43] FDA, *Information About Nitrosamine Impurities in Medications*, https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications (last visited July 5, 2021).

[44] *See* FDA, *Statement on the Agency's Ongoing Efforts to Resolve Safety Issue with ARB Medications*, https://www.fda.gov/news-events/press-announcements/statement-agencys-ongoing-efforts-resolve-safety-issue-arb-medications (Aug. 28, 2019).

prescribed antihypertensive medications are never actually started/taken by the patient in many cases (~20%),[45] and within one year nearly 50% of patients have discontinued their prescribed antihypertensive medication,[46] which suggests the patient impact of NDMA/NDEA found in valsartan is even less than forecasted by FDA.

In initiating their voluntary recalls of valsartan, manufacturers and the FDA warned physicians and patients not to discontinue valsartan use. As the FDA correctly explained: "[T]he risks of stopping taking an ARB product for treating high blood pressure and heart failure greatly outweighs the potential risk of exposure to trace amounts of nitrosamines."[47] In my experience, abruptly stopping antihypertensive medications such as valsartan can have a serious adverse result for the patient, including loss of blood pressure control, or in extreme situations, stroke or new onset or worsening heart failure. In my opinion, patients stopping their antihypertensive drug is a safety risk that outweighs any miniscule risk caused by further exposure to NDMA and/or NDEA until a readily available alternative ARB can be substituted or prescribed.

When the valsartan recalls occurred, physicians, including myself, had to find alternative treatment options for patients previously prescribed valsartan. In my personal experience, I did not witness any patients have an adverse effect as a result of the NDMA/NDEA impurities found in valsartan.

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[45] Fischer MA et al., Trouble getting started: predictors of primary medication nonadherence, Am. J. Med. 2011;124(11):1081.e9-1081.e1.081E22.
[46] Vrijens B et al., Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. BMJ. 2008;336(7653):1114-1117.
[47] *See* FDA, *Statement on the Agency's Ongoing Efforts to Resolve Safety Issue with ARB Medications*, https://www.fda.gov/news-events/press-announcements/statement-agencys-ongoing-efforts-resolve-safety-issue-arb-medications (Aug. 28, 2019).

VIII. Medical and Scientific Literature Does Not Support a Causal Relationship Between Trace Amounts of NDMA/NDEA in Valsartan and Cancer Development.

Based on my medical education, training, and experience, and my review of the medical and scientific literature and materials in this case, it is my opinion that there is insufficient scientific evidence to establish that trace amounts of NDMA or NDEA in valsartan caused the types of cancers Plaintiffs allege in this litigation. Plaintiffs' cancer disclosure lists various types of cancer: bladder, blood, breast, colorectal/intestinal, esophageal, gastric, kidney, liver, lung, pancreatic, pharyngeal, prostate, and uterine cancer.[48] However, in my education, training, and experience, patients prescribed valsartan do not develop those cancers at a higher rate than patients prescribed other antihypertensive medications. Moreover, I have conducted a thorough review of the relevant literature on valsartan use and cancer incidence, including the literature cited by Plaintiffs' experts in this litigation, and the literature simply does not support a causal association between exposure to trace amounts of nitrosamines in valsartan and cancer development. I will discuss my assessment of the key literature on this subject in turn:

Animal Studies Versus Human Exposure to NDMA/NDEA:

There are no direct human exposure studies for NDMA/NDEA in the published literature because it would be unethical to purposefully expose humans to a potential carcinogen. Thus, the only direct NDMA/NDEA exposure studies available are animal studies. However, there are vastly different exposures to NDMA/NDEA (per kg of body weight) between animals in the available studies and humans taking

[48] *See* Dkt. No. 706.

NDMA/NDEA-containing valsartan. This massively different exposure is demonstrated by the following exercise:

The European Medicines Agency estimated that a person taking NDMA-containing valsartan at the highest dose (320 mg) daily for seven years, based on the average level of impurity detected in the active substance from Zhejiang Huahai Pharmaceuticals (60 parts per million), that there would be one extra case of cancer per 5000 patients.[49] Over the course of 4 years (more likely time of ingestion of NDMA-containing valsartan), assuming that not one daily dose of valsartan was missed and that the patient remained on this maximum dosage of valsartan the entire time (consuming recalled valsartan with NDMA actually above the upper range of NDMA found in the recalled lots), the cumulative exposure would be 3,518,600 ng of NDMA and 504,200 ng of NDEA. For a 70 kg adult, the cumulative exposure would therefore be 50,266 ng/kg of NDMA and 7203 ng/kg of NDEA. In reality, actual exposures of individual patients are likely much lower due to differences in dosage of valsartan, missed doses, not remaining on valsartan for a full four years, and not all batches of valsartan having the same levels of NDMA or NDEA. Contrast these exposures to the much larger shorter-term exposures in animal models. A case in point is the study by Anderson and colleagues who administered a dose of 5 mg/kg of NDMA to male mice over 12 – 72 weeks, which caused lung tumors, with several-fold greater efficiency when ethanol was co-administered[50]; this dose, however, is

[49] European Medicines Agency, Update on review of recalled valsartan medicines: Preliminary assessment possible risk to patients, *available at* https://www.ema.europa.eu/en/news/update-review-recalled-valsartan-medicines-preliminary-assessment-possible-risk-patients (Aug. 2, 2018).
[50] Anderson LM et al., Characterization of ethanol's enhancement of tumorigenesis by N-nitrosodimethylamine in mice, Carcinogenesis 1992;13(11):2017-2111.

5,000,000 ng/kg of body weight and is ~100-fold greater of a dose of NDMA per kg body weight than the FDA estimated a human would have received over 4 years taking the maximal approved daily dose of valsartan (320 mg).

The remaining available animal studies on NDMA/NDEA exposure and cancer, which are listed on my materials reviewed list attached as Exhibit B, contain this and/or other flaws or factors that make direct extrapolation to humans highly problematic. For example, in addition to the vast differences in dose amounts mentioned above, animals in many of these studies were exposed to NDMA/NDEA through injection or other non-oral routes of administration, which are distinguishable from the oral ingestion used in the case of valsartan and directly impact metabolic processes. Thus, the direct extrapolation to humans of the tumorigenesis observed in animal studies, as Plaintiffs' experts have attempted to do in this litigation, is highly problematic.

Occupational Studies:

Plaintiffs' experts in this litigation also rely upon several studies of occupational exposure to nitrosamines that are distinguishable from potential exposure to NDMA/NDEA in valsartan, and therefore are not relevant to the issue of general causation.

In an article by Hidajat M et al., lifetime exposure to rubber dust, rubber fumes and N-nitrosamine with cancer mortality in a cohort of British rubber workers (N = 36,441 men) aged 35 and older, over 49 years (1967 – 2015) follow-up, was

reported.[51] Median age of the cohort was 50.1 years while the median age at death from cancers was 60 – 75 years. Cumulative lifetime exposure was reported for NDMA with cancer using a competing risk survival analysis. NDMA cumulative lifetime exposure was linked to a doubling of the risk for all cancers and cancers of the bladder, stomach, leukemia, multiple myeloma, prostate and liver. Similarly, lifetime cumulative exposure to rubber dust and rubber fumes were associated with increased mortality from all cancers and specifically cancers of the bladder, lung, stomach, leukemia, multiple myeloma, non-Hodgkins lymphoma, esopahagus, prostate, pancreas and liver.

This data in Hidajat M et al. shows that in nearly half a century of follow-up in occupationally exposed rubber workers the increased risk of cancer with NDMA exposure while simultaneously exposed to other carcinogens, rubber fumes and rubber dust, both of which exposed the workers to NDMA via inhalation, were also linked to increased cancer risk. There is minimal relevance of the findings of this study to the question of whether NDMA exposure via oral ingestion over a relatively short period of a few years caused excess cancer risk.

In McElvenny DM et al., mortality patterns in a British rubber workers cohort in men 35 years of age and older followed over 49 years (1967 – 2015) were compared to the male population of England and Wales using standardized mortality ratios.[52] SMRs > 1 mean there is higher than expected mortality in the rubber worker

[51] Hidajat M, McElvenny DM, Ritchie P, et al., Lifetime exposure to rubber dusts, fumes and N-nitrosamines and cancer mortality in a cohort of British rubber workers with 49 years follow-up, Occup. Environ. Med. 76(4):250-258 (2019).
[52] McElvenny DM, Mueller W, Ritchie P, et al., British rubber and cable industry cohort: 49-year mortality follow-up, Occup. Environ. Med. 75(12):848-855 (2018).

cohort while < 1 means there is lower than expected mortality in this same cohort. SMRs were significantly elevated, especially for cancers of the stomach (1.26), lung (1.25), and bladder (1.16); deaths from leukemia, non-Hodgkins lymphoma, and multiple myeloma, however, were not higher. Bladder cancer risk was higher only in workers exposed to 1-naphthylamine and 2-naphthylamine, both antioxidants. Overall there were 9227 cancer deaths; the SMR for all malignancies was 1.13. This SMR corresponds to 1062 excess cancer deaths over 49 years in the rubber worker cohort, or ~ 22 excess cancer deaths per year in men exposed to multiple potential carcinogens via multiple routes of exposure.

The McElvenny DM et al. study is not relevant to the question of whether short-term exposure to NDMA-containing valsartan tablets caused detectable excess cancer risk in exposed humans who orally ingested this medication. The inhalation route of exposure to rubber dust and fumes, the nearly half century of follow-up and the inability to isolate the impact of NDMA on study outcomes are all problematic.

Another occupational study relied upon by Plaintiffs' experts is Straif K. et al., which involved a cohort of 8933 rubber workers hired after January 1, 1950 who were still active or retired in January 1981 and were employed for at least one year at one of five study factories, and were followed for mortality from January 1, 1981 through December 31, 1991.[53] Work histories and cost-center codes were used to construct semi-quantitative exposures to nitrosamines (low, medium and high). Rate ratios (low = reference) for the medium and high exposure categories were constructed to

[53] Straif K, Weiland SK, Bungers M, et al., Exposure to high concentrations of nitrosamines and cancer mortality among a cohort of rubber workers, Occup. Environ. Med. 57(3):180-7 (2000).

estimate the risk of cancer. Nitrosamine exposure was significantly associated with an increased mortality from cancer of the esophagus, oral cavity and pharynx. No association was found between exposure to nitrosamines and cancer of the stomach or lung. There was a suggestion, though not statistically significant, of increasing mortality from cancer of the prostate and brain.

The reference group in the Straif K. et al. analysis was not a minimally to un-exposed group but rather had low estimated exposure to nitrosamines. Also, this group was a survivor cohort as they had to be hired after January 1, 1950 but also had to survive to January 1981 to be included in the reported follow-up. Again, there was no control of exposure to other potential carcinogens making it impossible to isolate the effect of any one exposure on the reported study outcomes. Thus, the reported findings in this study are of no consequence in understanding whether short-term exposure to NDMA-containing valsartan caused excess cancers as claimed.

Valsartan Studies:

Gomm et al. conducted a cohort study involving data collected from a German health insurance company involving patients who filled prescriptions for valsartan from 2012 to 2017.[54] Of the total 780,871 patients 40 years and older who had filled a prescription for valsartan in the specified time period, the authors found there was no association between exposure to valsartan containing NDMA and the overall risk of cancer nor was there a dose-response relationship between NDMA and cancer risk; also, there was no difference in cancer risk amongst those exposed to valsartan

[54] Gomm, W. et al., N-Nitrosodimethylamine-Contaminated Valsartan and the Risk of Cancer – A Longitudinal Cohort Study Based on German Health Insurance Data, at 357 (2021).

containing NDMA relative to those who filled prescriptions for valsartan that did not contain NDMA. However, the authors determined that "[a] statistically significant association was found . . . between exposure to NDMA-contaminated valsartan and hepatic cancer."[55] The age- and sex-adjusted risk of liver cancer was increased by ~4 cases/100,000 going from 34.6 cases to 39.1 cases/100,000. This study was a non-randomized retrospective, observational study of health insurance data. The study, as the authors admit, could not control for the many potential confounding factors (leads to residual confounding) that could have led to the erroneous statistical linkage of NDMA exposure to liver cancer in these patients.[56] Moreover, as the authors acknowledge, the study "can only state the existence of a statistical association[;] [c]ausality cannot be inferred."[57]

Another article by Al-Kindi et al. studied trends in adverse event reporting to FDA in the wake of the valsartan recalls.[58] The authors studied adverse events submitted through the FAERS database between January 1, 2017, and December 31, 2018, and compared the number of events as well as the percentage of neoplasm events reported by drug type (valsartan versus other ARBs). Authors found that following the 2018 recall, the number of adverse events increased more significantly for valsartan than for other ARBs, and the reporting odds ratio for neoplasm adverse events for valsartan increased from 1.7 pre-recall to 7.1 post-recall. The authors

[55] *Id.*
[56] *Id.* at 359 ("Although we adjusted our analysis by including numerous potential influencing factors, some risk factors for cancer, such as smoking habits, nutritional habits, and genetic predisposition, are not available in routine health insurance data and, therefore, could not be integrated into the analysis.").
[57] *Id.* at 360.
[58] Al-Kindi, S. et al., Abrupt Increase in Reporting of Neoplasms Associated with Valsartan After Medication Recall, Circ. Cardiovascular Qual. Outcomes, at 1 (2019).

specifically observed "an abrupt and biologically implausible rise in valsartan-associated neoplasms in the third quarter of 2018, after a drug recall that attracted extensive national media coverage."[59] Further underscoring the impact of the recall—and not a true causal association between valsartan use and cancer—the authors noted that "the duration of this effect was transient, as most cancer [adverse events] were reported early after the recall and decreased over time, remaining above baseline."[60] As the authors concluded: "[T]his observed phenomenon was likely associated with public alarm and fueled mainly by consumer and lay reporting. Government-sponsored strategies for patient and provider education are urgently needed to avoid premature discontinuation, legal disputes, and inaccurate drug-[adverse event] associations associated with valsartan and more broadly, with other recalled medical therapies."[61]

Finally, an article by Pottegard et al. presents the results of a Danish cohort study involving 5,150 patients with no history of cancer who used valsartan between January 1, 2012, and June 30, 2017.[62] The study followed patients for a median time of 4.6 years, and compared cancer outcomes in patients who used valsartan products potentially containing the unexpected NDMA impurity and patients treated with valsartan products that were not identified as being from one of the affected lots. The authors reported 198 cancer cases among patients taking valsartan potentially containing NDMA, and 104 cancer cases among patients not exposed to NDMA. The authors thus concluded that they "did not see an increased short term overall risk of

[59] *Id.*
[60] *Id.* at 2.
[61] *Id.*
[62] Pottegard, A. et al., Use of N-Nitrosodimethylamine (NDMA) Contaminated Valsartan Products and Risk of Cancer: Danish Nationwide Cohort Study, at 1 (2018) + Supplement.

cancer associated with the use of valsartan products potentially contaminated with N-nitrosodimethylamine (NDMA)."[63]

Thus, the available medical and scientific literature, including the animal studies on NDMA/NDEA exposure and occupational exposure studies, and publications examining the effect of NDMA/NDEA in valsartan, does not establish that trace amounts of NDMA or NDEA in valsartan cause an independent or increased risk of cancer.

IX. Shared Risk Factors Between Hypertension and Cancer Are More Likely to Have Contributed to Plaintiffs' Claimed Cancers Than Are Trace Amounts of NDMA or NDEA.

I have observed in my practice, having treated thousands of hypertension patients, several shared risk factors between hypertension and cancer, including smoking, alcohol, unhealthy diet, and lack of physical activity. Individuals with hypertension can be at a heightened risk of developing cancer because of the underlying risk factors often associated with both hypertension and cancer, medications used to treat hypertension, as well as medications used to treat common comorbidities such as diabetes, and perhaps due to hypertension itself. In terms of causality, these shared risk factors and exposures are significant and explain the putative association or correlation between NDMA/NDEA exposure in valsartan and cancer.

I do not believe it possible for an oncologist or other medical or scientific professional to say to a reasonable degree of medical or scientific certainty that the levels of NDMA or NDEA in therapeutic doses of valsartan between July 2012 and July

[63] *Id.* at 4.

2018 caused the cancers claimed by Plaintiffs,[64] or that valsartan increased the risk of the specific types of cancers alleged. There is no human clinical data showing that short-term exposure to valsartan potentially containing NDMA or NDEA was even associated with, much less caused, cancer in those exposed, as opposed to typically lifelong risk factors for both hypertension and cancer, such as smoking, alcohol intake, and lack of physical activity.

Nor do I believe it is possible for an oncologist or other medical or scientific professional to say to a reasonable degree of medical or scientific certainty that any Plaintiff would not have developed cancer if they had not taken valsartan medication.

X. Conclusion

My following opinions are based on grounds in scientifically and medically valid reasoning and methodology. Based on my medical education, training, and experience and my review of the medical and scientific literature and materials provided in this case, and to a reasonable degree of medical and scientific certainty, it is my opinion that:

1. The trace amounts of NDMA/NDEA found in valsartan do not independently cause, or increase the risk of, the types of cancers alleged by Plaintiffs;

2. No medical professional could credibly claim that Plaintiffs' cancers are caused by their use of valsartan, given the lack of corroboration of independent or

[64] Plaintiffs' cancer disclosure lists bladder, blood, breast, colorectal/intestinal, esophageal, gastric, kidney, liver, lung, pancreatic, pharyngeal, prostate and uterine cancer. *See* Dkt. No. 706.

augmented cancer risk in large human cohort studies using the same levels of NDMA/NDEA and conducted over a period of time similar to Plaintiffs' exposure;

3. No medical professional could credibly claim that any Plaintiff would not have developed cancer had they not taken valsartan; and

4. Hypertensive patients carry a higher incidence of cancer risk than the general population, and typically have comorbidities that are risk factors for various cancers—these factors are far more likely to cause cancer in a hypertension patient than short-term exposure to trace amounts of NDMA/NDEA in valsartan.

These are my opinions concerning the issue of general causation in this litigation. I have a sufficient factual basis and good grounds for my conclusions, and they are made to a reasonable degree of medical and scientific, and are based on my education, training, and experience.

I reserve the right to modify this report as additional information is provided to me, including but not limited to additional discovery and the depositions of Plaintiffs' experts which are ongoing.

I may use at trial any exhibits as a summary or in support of all of my opinions including: (1) any of the materials, or excerpts identified in this report and attachments, including the materials considered list; (2) excerpts from scientific articles or learned treatises; (3) demonstrative models; (4) exhibits used by Plaintiffs' experts, or other witnesses; and (5) any exhibit used in or identified at any deposition taken in this litigation. To the extent further information is disclosed or published, I will be happy to review it for consideration in modifying any portion of these opinions.

Dated: August 2, 2021

John Flack, M.D.